THE FIRST ADDENDUM

to the

Canadian Supplement, 1944, to the British Pharmacopoeia

Being DIVISION III of the
Regulations under the
FOOD AND DRUGS ACT

Made by Order in Council
P.C. 5754, 28th August, 1945

DEPARTMENT OF
NATIONAL HEALTH AND WELFARE
OTTAWA

THE FIRST ADDENDUM

to the

Canadian Supplement, 1944, to the British Pharmacopoeia

Being DIVISION III of the
Regulations under the
FOOD AND DRUGS ACT

Made by Order in Council
P.C. 5754, 28th August, 1945

DEPARTMENT OF
NATIONAL HEALTH AND WELFARE

OTTAWA

[P.C. 5754]

AT THE GOVERNMENT HOUSE AT OTTAWA

TUESDAY, the 28th day of August, 1945.

PRESENT:

HIS EXCELLENCY THE GOVERNOR GENERAL IN COUNCIL

WHEREAS the Canadian Committee on Pharmacopoedial Standards, appointed under the authority of Order in Council P.C. 4739, dated 9th day of June, 1942, has recommended the amendment of Schedule B to the Food and Drugs Act by the addition of certain material and the amendment of the Regulations established under the said Act (all as hereinafter set forth), which recommendation is concurred in by the technical officers of the Department of National Health and Welfare;

THEREFORE His Excellency the Governor General in Council, on the recommendation of the Minister of National Health and Welfare and under and by virtue of the Food and Drugs Act, is pleased to order as follows:—

1. Part V of Schedule B to the Food and Drugs Act is hereby amended by adding thereto the following material:—

"Digitalis, Digitalis Pulverata, Digoxinum, Injectio Ouabaini, Injectio Strophanthini, Ouabainum, Strophanthinum, Strophanthus, Tinctura Digitalis, and Tinctura Strophanthi."

2. Division III of the Regulations under the Food and Drugs Act was made and enacted by P.C. 9056 of 6th October, 1942, and as amended, is hereby further amended by adding thereto the 10 monographs hereto annexed.

3. The standards of quality and potency of the material hereby added to Part V of Schedule B to the said Act shall be as set out in the said monographs.

4. Part A of Division II of the said Regulations under the Food and Drugs Act is hereby amended by revoking the regulations, therein contained, entitled "Digitalis and the Preparations of Digitalis" and by substituting therefor the following:—

INJECTION OF DIGITALIS

Definition

1. Injection of Digitalis shall be a sterile solution of one or more of the glycosides or of the therapeutically desirable and cardio-active constituents of *Digitalis purpurea,* Linn, in sterilized water or in diluted alcohol. Either solvent shall be free from pyrogenic substances. It shall be sterilized by filtration as described in The British Pharmacopoeia, 1932 (p. 631).

Assay

2. The official method of assay shall be that employed in the Laboratory of Hygiene.

Labelling

3. See General Requirements, 1, and in addition, Injection of Digitalis shall be labelled to show the potency expressed as International Units per ml. The outer package shall bear a caution couched in the following or similar terms:

'*Caution.* One Digitalis unit given intravenously generally has a greater effect than the same amount given orally. Physicians are advised to take cognizance of this fact when administering Injection of Digitalis.'

Expiration Date

4. The expiration date shall be two years after assay.

A. D. P. HEENEY,
Clerk of the Privy Council.

DIGITALIS

(Digit.)

Digitalis

Synonyms.—DIGITALIS LEAF, DIGITALIS LEAVES.

Digitalis shall be the leaf of *Digitalis purpurea*, Linn., rapidly dried at a temperature between 55° and 60° as soon as possible after collection. Its potency shall not be less than 10 International Units per Gm. and its shall conform to the following specification with respect to characters and tests for purity.

Characters.

Macroscopic.—Digitalis consists of more or less crumpled or broken leaves, usually dark green on the upper surface and greyish on the under surface, owing to pubescence, and with the larger veins frequently purplish. As a rule, they vary from 10 to 30 centimetres in length and from 4 to 10 centimetres in width; in shape, they vary from ovate-lanceolate to broadly ovate, and petiolate. They have an irregularly crenate or serrate margin, decurrent at the base and sub-acute at the apex. The upper surface is hairy, the under surface densely pubescent and the veinlets reticulate.

Microscopic.—The upper epidermis has slightly wavy vertical walls, with few or no stomata. The under epidermis is similar, but with numerous stomata and many hairs; the hairs are frequently not attached, over irregular areas, to the cell structure within, especially near the veins. The hairs are simple, usually 3 to 5 cells in length, bluntly pointed and finely wavy. The glandular hairs consist usually of a unicellular pedicel bearing a one-celled or two-celled head. The chlorenchyma consists of a single layer of palisade cells and several layers of spongy parenchyma. There are numerous fibro-vascular bundles in the larger veins and in the petiole, and are separated by medullary rays one cell wide. The tracheae are annular, reticulate or spiral. Calcium oxalate and sclerenchymatous elements are absent.

Digitalis has a slight odour when dry, but peculiar and characteristic when moistened; the taste is decidedly bitter.

47391—2½

Tests for Purity.

Loss on Drying.—Digitalis loses, when dried at 100°, not more than 6 per cent of its weight.

Acid-insoluble Ash.—The acid-insoluble ash of Digitalis does not exceed 5 per cent of its weight.

Foreign Organic Matter.—Digitalis does not contain more than 2 per cent of foreign organic matter, including stems, browned leaves or flowers.

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Storage.

Digitalis should be kept in a well-closed container, which prevents access of moisture. It may be necessary to employ a device, containing a non-liquefying, inert, dehydrating substance to control the humidity.

Labelling.

The following items shall appear on the labels of packages and on immediate containers:—

(*a*) Name and address of manufacturer.
(*b*) The proper name, viz., Digitalis, Digitalis Leaf, Digitalis Leaves.
(*c*) The potency in terms of International Units per Gm.
(*d*) The lot number.

Preparations.

Digitalis Pulverata; Tinctura Digitalis.

NOTE.—When Digitalis, Digitalis Folia, Digitalis Folium or Pulvis Digitalis is prescribed, Digitalis Pulverata shall be dispensed.

DIGITALIS PULVERATA

(Digit. Pulverat.)

Powdered Digitalis

Powdered Digitalis shall be Digitalis dried at a temperature not exceeding 60° and reduced to a fine powder, of which all will pass through a number 60 standard mesh sieve and not more than 40 per cent through a number 100 standard mesh sieve. Its

potency shall be not less than 10 International Units per Gm. and it shall conform to the following specification with respect to test for purity.

For therapeutic administration, Powdered Digitalis must be assayed and adjusted to contain 10 International Units in 1 Gm. For this purpose Powdered Digitalis, containing more than 10 International Units in 1 Gm., may be adjusted to contain 10 International Units in 1 Gm. by thorough mixture with Powdered Digitalis, containing less than 10 International Units in 1 Gm. or with the exhausted marc remaining when Tincture of Digitalis has been prepared, the marc being carefully dried before mixing.

Test for Purity.

Loss on drying.—Powdered Digitalis loses, when dried at 100°, not more than 5 per cent of its weight.

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Storage.

Powdered Digitalis should be kept in a well-closed container, which prevents access of moisture. It may be necessary to employ a device, containing a non-liquefying, inert, dehydrating substance to control the humidity.

Labelling.

The following items shall appear on the labels of packages and immediate containers:—

(*a*) Name and address of manufacturer.
(*b*) The proper name, viz., "Powdered Digitalis."
(*c*) The potency in terms of International Units per Gm.
(*d*) The lot number.

Doses

Metric	Imperial
30 to 100 mgms.	½ to 1½ grains

Single Doses

0·2 to 0·6 Gm.	3 to 10 grains

Powdered Digitalis, for therapeutic administration, contains in 0·6 Gm. or in 10 grains, 6 International Units of activity.

NOTE.—Digitalis capsules, tablets and other dosage forms of Powdered Digitalis shall be labelled to show the potency in terms of International Units per dosage unit.

DIGOXINUM

(Digoxin)

Digoxin

$C_{41}H_{64}O_{14}$ Mol. Wt. 780.5

Digoxin shall be a crystalline glycoside obtained from the leaves of *Digitalis lanata,* Ehrh. and shall conform to the following specification with respect to characters and test for purity.

Characters.

Description.—Digoxin occurs as colourless, four-sided or five-sided tabular, odourless crystals.

Solubility.—Digoxin is almost insoluble in *water* and in *chloroform,* but soluble in dilute *alcohol.*

Constants.—The *melting point* of Digoxin is 265°, with decomposition; the *specific rotation,* determined by using a 2·0 per cent w/v solution in anhydrous pyridine and a mercury light, may vary from +13·5° to +13·7°.

Test for Purity.

Allied Glycosides.—Dissolve 1 mgm. of Digoxin in 1 mil of *glacial acetic acid* containing 0·01 per cent w/v of *ferric chloride* and add 1 mil of *sulphuric acid* so as to form a subjacent layer: a pure brown ring free from red colour is formed at the junction of the liquids. After a short time, the acetic acid acquires an indigo colour.

Sterilisation of a Solution.

A solution of Digoxin in Alcohol (70 per cent) is sterilized by *heating in an autoclave.* The container is sealed by fusion of the glass and is allowed to cool to room temperature before being opened.

Doses

Metric	Oral	Imperial
	Initial doses	
1·0 to 1·5 mgms.		1/60 to 1/40 grain
	Maintenance dose	
0·25 mgm. (twice daily)		1/250 grain (twice daily)
	By intravenous injection	
0·5 to 1·0 mgm.		1/120 to 1/60 grain

INJECTIO OUABAINI

(Inj. Ouabain)

Injection of Ouabain

Synonym.—Ouabain Ampoules.

Injection of Ouabain shall be a sterile solution of Ouabain in Sterilized Water free from pyrogenic substances. It shall be sterilized by *Tyndallization* or by *filtration* as described in the British Pharmacopoeia, 1932 (p. 631). It shall conform in other respects to the following specification.

Test for Purity.

Sterility.—Injection of Ouabain is sterile.

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Labelling.

The following items shall appear on the labels of packages and immediate containers:—

(*a*) Name and address of manufacturer.

(*b*) The proper name, viz., "Injection of Ouabain" or "Ouabain Ampoules".

(*c*) The potency, to be expressed in terms of mgms. of International Standard Ouabain per mil.

(*d*) The lot number.

(*e*) The expiration date, which shall be two years after the date of assay.

Storage.

Injection of Ouabain should be kept preferably in single dose, hermetically sealed ampoules, protected from light and heat.

Doses.

See under Ouabainum.

INJECTIO STROPHANTHINI

(Inj. Strophantin)

Injection of Strophanthin

Synonym.—STROPHANTHIN AMPOULES.

Injection of Strophanthin shall be a sterile solution of Strophanthin in Sterilized Water free from pyrogenic substances. It shall be sterilized by *Tyndallisation* or by *filtration* as described in The British Pharmacopoeia, 1932 (p. 631). It shall conform in other respects to the following specification.

Test for Purity.

Sterility.—Injection of Strophanthin is sterile.

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Labelling.

The following items shall appear on the labels of packages and immediate containers:—

(*a*) Name and address of manufacturer.

(*b*) The proper name, viz., "Injection of Strophanthin" or "Strophanthin Ampoules."

(*c*) The potency, to be expressed in terms of mgms. of International Standard Ouabain per mil.

(*d*) The lot number.

(*e*) The expiration date, which shall be two years after the date of assay.

Storage.

Injection of Strophanthin should be kept preferably in single dose, hermetically sealed ampoules, protected from light and heat.

Doses

See under Strophanthinum.

OUABAINUM

(Ouabain)

Ouabain

$C_{29}H_{44}O_{12}$, $8H_2O$. Mol. Wt. 728.5

Ouabain shall be a glycoside obtained from the seeds of *Strophanthus gratus* (Wall. et Hook.) Baillon. It shall correspond in potency to International Standard Ouabain and shall conform to the following specification with respect to characters, tests for identity and tests for purity.

Characters.

Description.—Ouabain occurs as white, odourless crystals or as a crystalline powder. It is stable in air, but is affected by light.

Solubility.—Ouabain is slowly soluble in about 75 parts of *water* and in about 100 parts of *alcohol (95 per cent)*, and is more soluble in hot *water* and in hot *alcohol (95 per cent)*.

Constants.—The *melting point* of Ouabain, previously dried at 130°, lies between 186° and 189°. In carrying out the test, preheat the bath to 170°. The *specific rotation* is not less than -31°, and not more than -32·5° when determined in a solution containing 1 Gm. of anhydrous Ouabain in 100 mils of *water*.

Tests for Identity.

Dissolve about 2 mgms. of Ouabain in 2 mils of *sulphuric acid*: a colour develops which is dark red by transmitted light and shows a greenish fluorescence by reflected light.

Dissolve about 0·1 Gm. of Ouabain in 5 mils of *dilute sulphuric acid* with the aid of heat and boil the solution for 1 or 2 minutes. The solution becomes brownish and turbid. Cool, filter and add to the filtrate 5 mils of *test solution of sodium hydroxide* and an equal volume of *water;* then add 3 mils of *solution of potassio-cupric tartrate* and boil: a red precipitate of cuprous oxide is formed.

Tests for Purity.

Reaction.—A 2 per cent w/v aqueous solution of Ouabain is neutral to *litmus paper*.

Alkaloids.—A 1 per cent aqueous solution of Ouabain yields no precipitate with *solution of tannic acid* or with *solution of iodine*.

Loss on drying and ash.—Ouabain loses, when dried at 130°, not less than 18 per cent and not more than 22 per cent of its weight; and leaves, on incineration, not more than 0·05 per cent of ash.

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Labelling.

The following items shall appear on the labels of packages and immediate containers:—

(*a*) Name and address of manufacturer.
(*b*) The official name, viz., "Ouabain".
(*c*) The lot number.

Storage.

Ouabain should be kept in a well-closed container, protected from light.

Preparation.

Injectio Ouabaini.

Dose.

(by intravenous injection)

Metric	Imperial
0·25 mgm.	1/250 grain

NOTE.—Ouabain is very poisonous and should not be tasted.

STROPHANTHINUM

(Strophanthin)

Strophanthin

Strophanthin shall be a glycoside or a mixture of glycosides obtained from the seeds of *Strophanthus Kombé,* Oliver. It shall posses in each mgm. a potency corresponding to 0·5 mgm. of International Standard Ouabain and shall conform to the following specification with respect to characters, tests for identity, and tests for purity.

Characters.

Description.—Strophanthin occurs as a white or yellowish powder containing varying proportions of water which is not lost entirely without decomposition. It is stable in air.

Solubility.—Strophanthin is soluble in *water* and in *alcohol (60 per cent),* but less soluble in *dehydrated alcohol.* It is almost insoluble in *chloroform,* in *ether,* and in *benzene.*

Optical Rotation.—An aqueous solution of Strophanthin is dextro-rotatory.

Tests for Identity.

When moistened with *sulphuric acid,* Strophanthin assumes an emerald-green colour, turning to brown.

To 5 mils of a 2 per cent w/v aqueous solution of Strophanthin add 1 drop of *test solution of ferric chloride* and 2 or 3 mils of *sulphuric acid*: a red precipitate is formed which turns green on standing for 1 or 2 hours.

Dissolve 0·1 Gm. of Strophanthin in 15 mils of *water* and add 5 mils of hot *solution of potassio-cupric tartrate*: no precipitate is produced.

Heat about 0·1 Gm. of Strophanthin with 5 mils of *dilute hydrochloric acid* to about 70°: a precipitate of strophanthidin is formed. Cool, filter and add to the filtrate 5 mils of a mixture of *test solution of sodium hydroxide* and an equal volume of water: then add 3 mils of *solution of potassio-cupric tartrate* and boil: a red precipitate of cuprous oxide is formed.

Tests for Purity.

Reaction.—An aqueous solution of Strophanthin is neutral to *litmus paper.*

Ash.—Strophanthin leaves, on incineration, not more than 0·05 per cent of ash.

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Labelling.

The following items shall appear on the labels of packages and immediate containers:—

(*a*) Name and address of manufacturer.

(*b*) The official name, viz., "Strophanthin".

(*c*) The lot number.

Storage.

Strophanthin should be kept in a well-closed container, protected from light.

Preparation.

Injectio Strophanthini.

Dose.

(by intravenous injection)

Metric	Imperial
0·5 mgm.	1/120 grain

NOTE.—Strophanthin is very poisonous and should not be tasted.

STROPHANTHUS

(Strophanth.)

Strophanthus

Strophanthus shall be the dried, ripe seed of *Strophanthus Kombé,* Oliver or of *Strophanthus hispidus,* De Candolle, freed from the awns. Its potency per Gm. shall correspond to not less than 42 mgms. of International Standard Ouabain and it shall conform to the following specification with respect to characters, test for identity and test for purity.

Characters.

Macroscopic.—1. *S. Kombé.* The seeds of S. Kombé are oblong-lanceolate, flattened and obtusely edged, varying from 8 to 25 millimetres in length, from 2·5 to 5 millimetres in width, and from 0·5 to 2 millimetres in thickness. The raphe edge extends from near the centre to one side of the apex. The seeds are mostly pale yellow, with a greenish tinge, some being brown to light olive and are covered with longitudinal rows of closely appressed hairs directed to the apex. The kernel is grayish-white and oily, the cotyledons straight and the endosperm narrow.

2. *S. hispidus.* The seeds of S. hispidus are similar in character, except that the colour is light-brown to dark-brown, the size somewhat smaller and the hairs fewer and shorter.

Microscopic.—The epidermis of the testa is composed of elongated, polygonal cells, with straight, thickened and lignified side walls, many being extended to form hairs with a longitudinal lignified rib, and band shaped thickening at the base. The endosperm consists of 9 to 30 rows of parenchymatous cells. In the testa may be found scattered cluster crystals and an occasional single crystal of calcium oxalate, and in the endosperm and cotyledons fixed oil, aleurone grains and starch grains from 4 to 8 microns in diameter.

Strophanthus has a characteristic odour and a very bitter taste.

Test for Identity.

Moisten a cut seed or a portion of powder with *sulphuric acid;* an olive green to yellowish green colour is produced.

Test for Purity.

Ash.—The ash of Strophanthus does not exceed 5 per cent

Assay.

Carry out the official method of assay employed in the Laboratory of Hygiene.

Preparation.

Tinctura Strophanthi.

Doses

Metric	Imperial
30 to 60 mgms.	½ to 1 grain

TINCTURA DIGITALIS

(Tinct. Digit.)

Tincture of Digitalis

Tincture of Digitalis shall be prepared from the following ingredients in the amounts specified and its potency shall be one International Unit per mil.

Digitalis, in No. 40 powder, 100 Gm.

Alcohol, 70 per cent, a sufficient quantity.

Prepare 900 mils of a tincture by the Percolation Process as described in The British Pharmacopoeia, 1932 (p. 436).

Assay a portion of the tincture by the official method employed in the Laboratory of Hygiene. To the remainder of the tincture add a sufficient quantity of Alcohol (70 per cent) to produce a Tincture of Digitalis of a potency of one International Unit per mil.

Alcohol Content.

The alcohol content of Tincture of Digitalis is not less than 65 per cent nor more than 70 per cent v/v of ethyl alcohol.

Labelling.

The following items shall appear on the labels of packages and immediate containers:—

(*a*) Name and address of manufacturer.

(*b*) The proper name, viz., "Tincture of Digitalis".

(*c*) The potency, viz., "Contains 1 International Unit per mil."

(*d*) The lot number.

(*e*) The expiration date which shall be two years after the date of assay.

Doses.

Metric	Imperial
0·3 to 1 mil	5 to 15 minims
Single Dose	
2 to 6 mils	30 to 90 minims

Tincture of Digitalis contains in 6 mils, or in 90 minims, 6 International Units.

TINCTURA STROPHANTHI

(Tinct. Strophanth.)

Tincture of Strophanthus

Tincture of Strophanthus shall be prepared from the following ingredients in the amounts specified and shall be of such potency that the specific activity of one mil corresponds to that of 4·2 mgms. of International Standard Ouabain.

Strophanthus, in No. 40 powder, dried at 45°	100 Gms.
Alcohol (70 per cent),	a sufficient quantity.

Pack the powder in a percolator; moisten with *light petroleum (boiling-point, 50° to 60°)*, and macerate for twenty-four hours; allow percolation to proceed, continuing the addition of *light petroleum (boiling point, 50° to 60°)*, until the liquid passes through colourless. Reject the percolate, remove the marc from the percolator, and dry it by exposure to air, finishing the drying, if necessary, in a current of

air at a temperature not exceeding 40°. Again reduce it to powder, repack in the percolator, and moisten with Alcohol (70 per cent). Macerate for forty-eight hours, then pour on successive quantities of Alcohol (70 per cent), percolating slowly, until 500 mils of the percolate are obtained.

Assay a portion of the percolate by the official method of assay employed in the Laboratory of Hygiene. To the remainder of the percolate add sufficient Alcohol (70 per cent) to produce a Tincture of Strophanthus of the required degree of activity.

Assay.

Carry out the official method of assay employed by the Laboratory of Hygiene.

Alcohol Content.

The *alcohol content* of Tincture of Strophanthus is not less than 67 per cent and not more than 70 per cent v/v of ethyl alcohol.

Labelling.

The following items shall appear on the labels of packages and on immediate containers:—

(*a*) Name and address of manufacturer.

(*b*) The proper name, viz., "Tincture of Strophanthus."

(*c*) The potency, viz., "Each mil corresponds in potency to 4·2 mgms. of International Standard Ouabain.

(*d*) The lot number.

(*e*) The expiration date which shall be two years after the date of assay.

Doses

Metric	Imperial
0·12 to 0·5 mil	2 to 8 minims